FURTHER OBSERVATIONS ON AMINOPTERIN FOR PSORIASIS*

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Aminopterin (4-amino-pteroylglutamic acid) is not to be recommended lightly for the treatment of psoriasis, and indeed there are those who feel it should not be used at all (1). On the other hand, psoriasis may be disabling and life-ruining. There are perhaps 4 million individuals in this country who suffer with this disorder. The benefits of the drug are brought about by its toxic effect, and about one-fifth of individuals who take it according to schedules used by us do have disagreeable symptoms such as: aphthous stomatitis, gastrointestinal distress, temporary intensification of lesions, temporary partial hair loss, and temporary leukopenia. In addition, we have learned to be very cautious in using aminopterin in the following situations: universal erythroderma (due to psoriasis), involvement of stasis dermatitis with psoriasis, intertriginous psoriasis, and in small, frail, aged or debilitated individuals. Last but not least, the drug must never be given during pregnancy as it is an abortifacient and might induce fetal malformations (2). Indeed there is serious question as to whether it should ever be given to a woman of childbearing age.

RATIONALE

The rationale for its use is as follows: psoriasis appears to be an hereditary tendency (3, 4) for excessive epithelial activity, usually in localized sites, leading to overproduction of horny cells which tend to accumulate.

To Gubner (5) must go the credit for first pointing out that aminopterin may be beneficial in psoriasis, and that its epithelial-inhibiting effect may be more pronounced than its suppressive action on blood forming organs. Others besides ourselves have confirmed Gubner's observations (6, 7). We were able to confirm the epithelial-suppressing effect by demonstration of a marked cytotoxic action on monkey kidney epithelium in tissue culture (8).

Aminopterin interferes with folic acid metabolism. More specifically, it interferes with conversion of folic acid to citrovorum factor, which is its biologically active form. This nonavailability of the citrovorum factor interferes with the biosynthesis of purines and pyrimidines, which are important structural components of nucleic acids, the interconversion of glycine and serine, and transmethylation reactions (9).

The action, then, of aminopterin is to regulate the too-rapid epithelial cell reproduction in psoriasis, bringing about a replacement of psoriatic plaques by normal skin. Normal epithelial growth is unaltered because suppression usually requires a dosage of aminopterin in excess of that used for the treatment of psoriasis.

DOSAGE SCHEDULES

We have attempted to find safe, effective dosage schedules. The range between benefit and toxicity is narrow. Aminopterin is marketed in 0.5 mg. tablets for oral use. It should not be prescribed, but must be given directly to the patient, with explicit instructions as to use. It is our custom to give the patient no more than 12 of the 0.5 mg. tablets at one time. Five dosage schedules have been used, as follows:

I. one 0.5 mg. tablet by mouth daily for 6 days.
II. as in I, but repeated after one week.
III. one daily for 12 days.
IV. two daily for 6 days.
V. two daily for 3 days. Then one daily for 6 days.

These courses may be repeated from time to time as indicated, with suitable intervening rest periods. The patient is cautioned to discontinue the treatment at once if any untoward effect whatsoever occurs. Blood counts are performed frequently.

RESULTS

In 1955, we reported results of treatment of 171 psoriatic patients with aminopterin (8), the majority taking the drug according to schedules II, III, or IV. Approximately 42% experienced clearing of their lesions, although there was a distressing tendency for the lesions to reappear

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TABLE I

Results of Aminopterin Treatment of 329 Psoriasis Patients

Schedule	No. of Cases	Response		
		75–100%	50–75%	0–50%
I	23	13	6	4
II	50	25	16	9
III	175	99	38	38
IV	35	19	8	8
V	46	30	13	3
Total	329	186	81	62

TABLE II

Frequency of Courses

One course	44 (13 with no benefit)
Every 3 weeks	68
Monthly	77
6 weeks–2 months	55
2–4 times a year	72
Once yearly	12
Once every 3 years	1
	329

TABLE III

Over-All Toxic Effects

Schedule	I	II	III	IV	V
Patients Treated	23	50	175	35	46
Aphthous lesions	1	2	27	9	4
Intensification or erosions of the lesions	0	2	9	4	3
Transient partial alopecia	1	0	4	3	2
Gastrointestinal symptoms	0	1	4	2	1
Leukopenia	0	0	2	2	0
Miscellaneous	0	1	1	0	0
Total reactions	2	6	47	20	10
Total patients with reactions	2	6	42	11	9

within a short time (1–2 weeks in most instances). About 14% of them had toxic effects, mostly of a transitory and mild nature.

An additional 42% noted some improvement, leaving only 16% (approximately) who had no benefit.

For the purpose of the present study, the records of the original 171 patients were reviewed and brought up to date as of April, 1958. By this time, many of the original patients had been retreated, using the same or more vigorous dosage schedules. Moreover, data on 158 additional patients had become available, bringing the total to 329.

As shown in Table I, approximately 57% of these patients noted 75–100% response and another 25% had 50–75% improvement. About 18% had insufficient benefit to warrant re-use of this potentially dangerous drug.

Frequency of Courses. It was necessary to repeat the course of treatment, as shown in Table II. Only one course was given to 44 patients, 31 of whom had lasting benefit.

Toxic Effects. As shown in Table III, toxic effects occurred in 70 of 329 patients, an over-all incidence of 21%. Roughly speaking then, one patient in five may be expected to have one or more toxic effects.

Under "Miscellaneous Reactions" there was one patient with recurrent mastitis and another with bleeding from the kidney. The latter occurred in a 52 year old man on each of two occasions after taking one 0.5 mg. tablet daily for 12 days. The episodes of hematuria commenced on the 12th day after completion of the course of treatment and lasted several days on each occasion. According to the urologist, the renal calyx was the source of bleeding.

There were four instances of leukopenia (WBC below 5000/cu.mm. ranging between 2300 and 4300 WBC/cu.mm.). In three of these patients the WBC had returned to normal by the time the count was repeated. The fourth patient had leukopenia persisting for 3 months at the time of this report. His hematologist attributes this to hypersplenism and not aminopterin. The bone marrow was normal. Two of these four patients had taken only 6 mg. of aminopterin. There were no instances of anemia. Although hundreds of bloodcounts have been performed, we consider the data here to be incomplete because practically all of our patients were treated on an ambulatory basis, and a leukocyte depression may have been missed in many instances.

One patient had an episode of "heat stroke" within three weeks after taking a course of aminopterin (Schedule III). He had extensive psoriasis and was working in the sun during hot weather. He has subsequently taken aminopterin

without difficulty. It seems likely that this episode was due to extensive anhidrosis (10).

A generalized scarlatiniform rash occurred in a 40 year old woman after she took one 0.5 mg. tablet. However, she was taking other medications, including reserpine, at the time. If the rash were due to aminopterin, it would be the only instance of idiosyncrasy, as opposed to direct toxic effect, that we have encountered.

Two patients suffered bowel obstructions within a few weeks of taking aminopterin, requiring surgical intervention. One patient has taken repeated courses of aminopterin subsequently without trouble. One patient had a strangulated hernia which may have been coincidental, because of a time lag in relationship to taking the drug.

The most alarming complications encountered were reported in a previous study, and consisted of a combination of leukopenia, fever, epithelial sloughs and temporary hair loss (8). We have not seen more instances of reactions this severe, probably because of our greater familiarity with limitations of the drug.

It would now appear to be unnecessary to rely upon administration of citrovorum factor for reactions to aminopterin, as discussed in a previous report. Rather, it is important to initiate treatment with a conservative schedule, and also to discontinue treatment promptly whenever there is the slightest hint of a toxic reaction. The citrovorum factor ("Leucovorin") is available in 1 cc. ampules containing 3 mg. for intramuscular use. In case of a severe toxic reaction it may be given daily until remission is achieved.

Long Term Results

In this group of 41 patients 28 experienced 75–100% clearing of lesions, 12 had 50–75% benefit, and one had only 25–50% benefit (Table IV). Obviously, this was a highly selected group in the sense that they would not have continued to take repeated courses for months and years if the treatment had not been worthwhile.

Eighteen of them were men and 23 were women; the average duration of the disease was 21 years; prior treatment had included "everything" and they had concluded, in the word of one patient, that the situation was "hopeless".

Toxicity—Long Term Group

These patients were treated over a period of one to five years. All of these 16 patients were able to resume treatment despite these temporary ill effects (Table V).

TABLE IV

Long Term Results (41 Patients)

Total dose: 100 mg. (200 tablets) or more. Average dose: 197 mg. (maximum 348 mg.)

Schedule	I	II	III	IV	V
Number of Patients	1	2	20	5	13

Frequency of Repetition of Courses	
3 week interval	8 patients
monthly interval	20 patients
6 week–2 month interval	10 patients
2–4 times per year interval	3 patients

TABLE V

Toxicity—Long Term Group (41 patients)

16 patients—39%

Sore mouth	10
Intensification	2
Gastrointestinal symptoms	2
Hair loss	1
Leukopenia	1

TABLE VI

Analysis of Data of Patients Having 75–100% Response

I. 186 out of 329 cases
II. 57% of those treated
III. Schedules

	I	II	III	IV	V	Total
Cases	13	25	99	19	30	186
Reaction	2	1	33	9	7	52

IV. 28% had toxic reactions

Patients Having 75–100% Response

It is evident from Table VI that patients having an excellent response are more likely to have concomitant temporary toxic effects than those having less than a 75–100% response. It is also evident that one need not necessarily take the medication according to the most vigorous schedule (V and IV) in order to have such a response. Such figures naturally would have to be corrected for such factors as the weight of the patient and the type of involvement; but in general, the need for varying the dosage schedule according to the response of the lesions and the tolerance of the patient is borne out by these figures. It will be seen also that administration of

Schedule IV was accompanied by an almost prohibitively high incidence of reactions (47%).

Drug Resistance

The question of whether an individual may obtain a satisfactory temporary response to the administration of aminopterin, and then fail to respond to readministration cannot be answered clearly. Some 19 individuals appeared to have developed resistance, 14 of these having had 75–100% benefit originally, and 5 of them 50–75% benefit. Twelve of them failed to respond subsequently even though they took the drug according to two or three of the more vigorous schedules (III, V and IV). The other seven patients in this "resistant" group appeared to respond well to administration subsequently of a more vigorous treatment schedule.

Enduring Benefit with Small Doses

Thirty-one patients enjoyed remissions of a year or more after taking a single course of aminopterin. In other words, about 9% of the entire group of patients derived lasting benefit from 6 mg. or less. It must be admitted that one might reasonably expect spontaneous remissions in this small a percentage of a group of psoriatic patients. Osborne, for example, points out that as many as 20–30% may experience spontaneous clearing of their lesions in a 6 to 12 month period (11). On the other hand, the average duration of the disease in this group was eight years, ranging from six months to 30 years, and the disease had not yielded to conventional therapy.

Other Antimetabolites

Daraprim (2,4-diamino-5-*p*-chloropteroyl-6-ethyl-pyrimidine), which is a potent folic acid antagonist, and which has a suppressive effect on erythrocytes, was given to 12 psoriatic patients in a dosage of 25 mg. daily for one month, without benefit or significant ill-effect. Similar lack of response was noted with purinethol (6 mercapto purine), a synthetic analogue of adenine (a nucleic acid constituent) and of the purine base hypoxanthine. This drug is purported to interfere with nucleic acid biosynthesis. It was administered orally to 12 patients in a dose of 50 mg. four times daily for six days.

DISCUSSION

The approach to management as outlined in this study obviously is not the answer to the psoriasis problem. However, it does focus attention upon a possible approach in research. The thesis upon which much effort has been expended in the past, namely, that psoriasis is based upon faulty fat metabolism and pancreatic insufficiency, has (in our opinion) at long last been laid to rest (12, 13).

We feel that the present study may encourage further investigation into the metabolism of the epithelial cell itself, with the thought that there might be some inherent metabolic defect or fault in epithelial cell reproduction in psoriasis. Recent work has shown a localized defect in protein metabolism in the psoriatic lesion, presumably due to lack of dipeptidase activity, resulting in a lowered content of water-binding free amino nitrogen and elevated sulfhydryl content in the scale. Some investigators feel that the dipeptidases are inhibited by a substance, not yet defined, in the scale (14). Others feel that instead of an inhibitor, there is lack of an enzyme activator (15). In any event, the non-functioning dipeptidases are present, as has been shown by stimulating their activity with cobalt (16). One may speculate as to whether there is a specific defect in protein metabolism in psoriasis, or whether the abnormalities in protein metabolism are the result of the greatly accelerated growth of epithelial cells in this disease. Suffice it to say, for the purposes of this report, that aminopterin undoubtedly exerts its benefit in psoriasis because of its antianabolic activity.

The practicality of this approach is limited by the dangerous potentiality of aminopterin, and by certain absolute contraindications. However, in the words of one authority, there are only two internal medications which may fairly regularly benefit psoriasis, these being inorganic arsenic and aminopterin (17). To these may possibly be added some newer corticosteroids, such as triamcinolone and methylprednisolone, but of course the use of these compounds is not without hazard also.

SUMMARY AND CONCLUSIONS

The 1955 report on the use of aminopterin in treatment of psoriasis is augmented and certain clinical aspects are inquired into in more detail. The theme of this study, as before, is an attempt

to show that conservative dosages of aminopterin may clear or improve lesions of psoriasis without incurring too high an incidence of toxic effects. Aminopterin was administered to 329 individuals with psoriasis according to schedules used in a previous study. Approximately 57% of these patients noted 75–100% clearing of their lesions, and another 25%, approximately, had 50–75% clearing. This makes a total of 82% having enough benefit to make the treatment seem worthwhile. The over-all incidence of toxicity was found to be about 21%, although patients having an excellent response had an incidence of reactions of about 28%. This substantiates the view that benefit is brought about largely by toxic effect. A special group of 41 patients was singled out for study of longterm effects of aminopterin given in repeated courses. Each of these patients took in excess of 100 mg. of aminopterin during a time period of one to five years. While the incidence of toxic effects was over 39%, these were mild, and did not interfere with readministration of the drug.

Other points touched upon in this study include a discussion of potentially serious reactions, analysis of data in patients having 75–100% response, inquiry into the question of drug resistance, presentation of data regarding enduring benefit with small doses in some of the more fortunate patients, and the lack of response of psoriasis to two other antimetabolites.

Controls in this study were provided as follows:

1. All of the patients had treatment-resistant psoriasis, so far as conventional methods are concerned.

2. The results of treatment with various dosage schedules of aminopterin are compared.

3. A comparison of the results with two other antimetabolites, both of which failed to bring about any benefit in a group of 12 patients each, thereby providing a baseline.

As in a previous report, no attempt is made to urge trial of this approach in the treatment of psoriasis other than on a well controlled investigative basis.

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DISCUSSION

Dr. Harvey Blank (Miami, Florida): A patient in our institution with psoriasis and leukemia was treated with Myleran with spectacular clearing of the psoriasis. Myleran® (busulfan) is less toxic than aminopterin. It is given in doses of two two-milligram tablets (4 mg.) a

half hour before breakfast every day, for four to six weeks before deciding whether the drug has an effect or not. Weekly white and platelet counts are essential. Our results are not as dramatic as those to aminopterin. Perhaps a third responded and another third improved up to a certain point and the other third not at all. It is a safer drug but still only an interesting experimental tool. I want to ask Dr. Bennett if he has had any experience with this particular agent?

DR. CLARENCE S. LIVINGOOD (Detroit, Michigan): I would like to ask Dr. Bennett about the concentration of the aminopterin which was used in the tissue culture toxicity studies. Dr. Funan Hu and others in our Department have worked in this field for many years and the minimum toxic concentrations in tissue culture studies of a great many drugs have been determined and correlated with clinical results. I don't believe that this is a particularly good method of determining the toxicity of a drug and I would tend to disregard these results for aminopterin in attempting to estimate its toxicity.

DR. EUGENE J. VAN SCOTT (Bethesda, Md.): Did any other hemologic changes occur in these patients, such as depression of the number of platelets or reticulocytes?

In any consideration of casual therapeutic use of metabolic antagonists in psoriasis perhaps we should keep in mind possible mutagenic effects of these drugs.

DR. JAMES H. BENNETT (in closing): I was quite interested in Doctor Blank's remarks. We are glad to see that other antimetabolites are being tried. We have had no personal experience with Myeleran.

In answer to Doctor Livingood's question, the dilution we used was 0.1 mg. of aminopterin per ml. of liquid nutrient medium. This work was reported in our previous paper (Rees, R. B.; Bennett, J. H.; and Bostick, W. L.: Aminopterin for Psoriasis, A.M.A. Arch. Dermat. 72: 133 (Aug.) 1955).

In answer to Doctor Van Scott's question, the platelet counts were done only occasionally when there had been a severe reaction or when a leukopenia was present. Routinely we checked just the normal complete blood count.

In answer to the question of aminopterin possibly inducing leukemia, we have no information on this subject.